



## Vultures and diclofenac

The oriental white-backed vulture (*Gyps bengalensis*) has a brownish black plumage, and a naked scrawny neck accompanied with a white ruff of soft feathers around the base. A patch of white plumage on the back can be seen when it takes off.

It roosts in trees along rivers, barrages, canals, cultivations, and particularly slaughterhouses, because it feeds exclusively on carrion. It is a common, resident vulture of Pakistan and India.

Starting in the 1990s, catastrophic population declines noted in India have continued across the subcontinent, and have included other vulture species. Surveys in Pakistan [1] have shown mortality in adults and young to be as high as 86%, with population declines as high as 95% between 2000 and 2003.

The reason appears to be that diclofenac has become widely used in veterinary practice. The residues appear in carcasses, and the vultures feed off the carcasses, or whatever parts are available from slaughterhouses. Whatever good the diclofenac does for the animals to whom it is administered, it does major harm to the vulture, causing renal failure [1]. Interesting though this is, it has a point. That point is that we sometimes get effects for which we had not bargained, and that adverse events are important.

## Internet interest

OK, we live in the Internet age. So how is medicine and healthcare adapting to these new ways? A quick search revealed little evidence of much happening, but two jewels of studies from Korea and the USA provide real insight into how we can do things better, faster, and cheaper. More examples please!

Reference:

- 1 JL Oaks et al. Diclofenac residues as the cause of vulture population decline in Pakistan. *Nature* 2004 427: 596-598.

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## TOPICAL NSAIDs FOR OA: UPDATE

Bandolier 110 had an updated look at topical NSAIDs. 2004 has seen an upsurge of publications, with three recent systematic reviews and several new randomised trials. The current state of knowledge has been summed up on the new Bandolier Internet section on topical analgesics, but briefly for topical NSAIDs it comes down to the following:

- Topical NSAIDs can penetrate skin and underlying tissues, with ketoprofen and diclofenac amongst the most likely to be effective based on laboratory experiments.
- Topical NSAIDs are found in high concentration in the knee joint (particularly meniscus and cartilage).
- Topical NSAIDs produce much lower plasma concentrations than oral NSAIDs, typically 5% of oral concentrations or less.
- In strains and sprains over seven days, topical ketoprofen is probably better than other topical NSAIDs, and topical indomethacin is not significantly better than placebo.
- In chronic musculoskeletal pains, topical NSAIDs are better than placebo at two weeks, but confidence is limited by the short duration of trials.

The main unknown is in chronic conditions, where larger, longer trials have been needed to give confidence in longer-term efficacy of topical NSAIDs. In particular, direct comparison of the same NSAID in topical and oral formats has been missing. We now have three large randomised trials [1-3] against placebo and oral NSAID that increase our confidence substantially.

## Placebo control, 4 weeks [1]

This trial was properly randomised (independent computer-generated allocation), with concealed allocation, and identical controls to maintain blinding. Patients had primary osteoarthritis in at least one knee verified radiologically within the previous six months, at least moderate pain, and aged 18 to 80 years. There were sensible exclusion criteria such as use of oral NSAIDs. Assessments were made at baseline and after four weeks, and the trial outcomes accorded with those of the latest advice on trials in arthritis.

Three topical treatments were tested: topical diclofenac in dimethylsulphoxide (DMSO), DMSO without diclofenac (vehicle), and a placebo without either diclofenac and with a low concentration of DMSO. A monitored amount of solution was applied to the knee being treated in a standard way, without rubbing, four times daily.

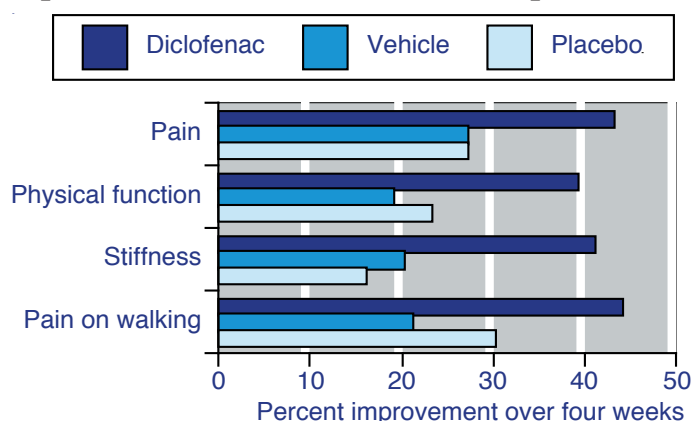
## Results

There were 248 patients in the three groups, and the groups were well matched at baseline, being about 60% women with an average age of about 62 years. Almost 90% completed the four weeks of treatment. The main reasons for withdrawal were lack of effect in vehicle and placebo groups (8/80 and 10/84 respectively), and adverse events with topical diclofenac (5/84) and vehicle (3/80).

WOMAC scores for pain, physical functioning, stiffness, and pain on walking all fell significantly more with topical diclofenac than vehicle or placebo (Figure 1). Patient global assessment was significantly better with topical diclofenac than vehicle or placebo.

Dry skin (36%) and rash (11%) were more frequent with topical diclofenac than vehicle or placebo. There was no difference in gastrointestinal or other adverse events.

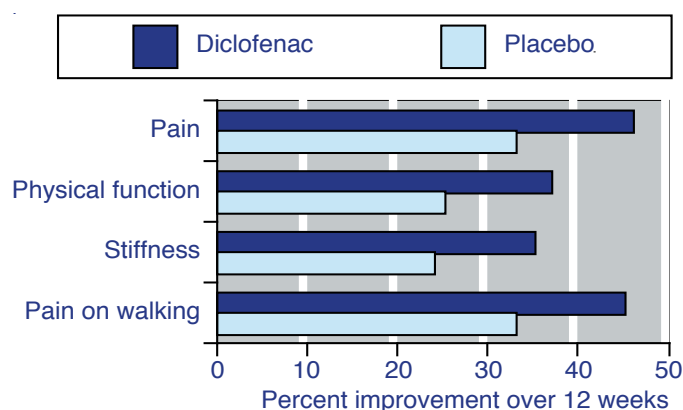
**Figure 1: Results of four-week comparison of topical diclofenac with vehicle and placebo**



## Placebo control, 12 weeks [2]

The basic design features of this trial were as for the four-week study, with efficacy measured after 12 weeks. A monitored amount of solution containing diclofenac or vehicle placebo control identical but without diclofenac was applied to the knee being treated in a standard way without rubbing, four times daily.

**Figure 2: Results of 12-week comparison of topical diclofenac and placebo**



## Results

Randomisation involved 326 patients, and treatment and placebo groups were well matched at baseline, being about 68% women with a mean age of 64 years. With placebo and topical diclofenac the main reason for withdrawal was lack of efficacy (42/162; 26% and 28/164; 17% respectively). Adverse event withdrawals were rare (4/162 and 8/164 respectively).

WOMAC scores for pain, physical functioning, stiffness, and pain on walking all fell significantly more with topical diclofenac than vehicle placebo control (Figure 2). Patient global assessment was significantly better with topical diclofenac than vehicle placebo control.

Local adverse reactions of dry skin and rash occurred more frequently with topical diclofenac than with vehicle control (37% vs 25% and 11% vs 5% respectively). Gastrointestinal adverse events were rare and occurred no more frequently with topical diclofenac than with placebo.

## Oral control, 12 weeks [3]

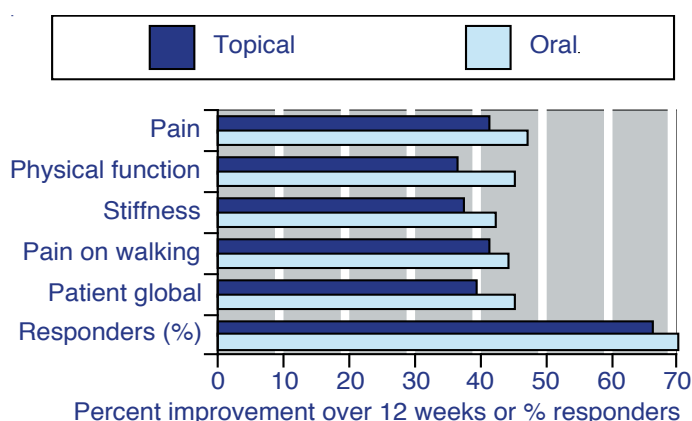
The basic design features of the third study were similar to the placebo-controlled trials, except that here the design was double-dummy, with oral diclofenac 150 mg daily or oral placebo and topical diclofenac or topical placebo arranged so that topical and oral diclofenac were directly compared. Topical or oral diclofenac were used three times daily for 12 weeks, and only one knee, that with the highest pain score at baseline, was used for efficacy measurement.

## Results

The 622 patients randomised had an average age of 64 years and 58% were women. The two groups were well matched at baseline. Sixty-one percent completed the 12 weeks. Of those withdrawing, adverse events contributed 20% with topical and 25% with oral diclofenac, while lack of efficacy contributed 9% and 3% respectively.

WOMAC scores for pain, physical functioning, stiffness, pain on walking, patient global assessment, and number of responders were similar with topical and oral diclofenac (Figure 3) using an intention to treat analysis, or a per protocol analysis. A responder was defined as a patient with a

**Figure 3: Results of 12-week comparison of topical and oral diclofenac**



**Table 1: Adverse events over 12 weeks with topical and oral diclofenac**

Adverse event	Number (%) with		Relative risk (95% CI)	NNH (95% CI)
	Topical diclofenac (311)	Oral diclofenac (311)		
All reported				
Dyspepsia	48 (15)	81 (26)	0.6 (0.4 to 0.8)	9 (6 to 23)
Abdominal pain	36 (12)	67 (22)	0.5 (0.4 to 0.8)	10 (6 to 24)
Diarrhoea	27 (9)	54 (17)	0.5 (0.3 to 0.8)	12 (7 to 29)
Severe				
Dyspepsia	2 (0.6)	11 (3.5)	0.2 (0.04 to 0.8)	35 (19 to 152)
Abdominal pain	2 (0.6)	13 (4.2)	0.2 (0.03 to 0.7)	28 (17 to 88)
Diarrhoea	1 (0.3)	9 (2.9)	0.1 (0.01 to 0.9)	39 (22 to 165)
All severe	5 (1.6)	33 (11)	1.2 (0.06 to 0.4)	11 (8 to 19)

50% or greater improvement in pain or function that was 20 mm or more on a 100 mm VAS, or 20% or greater improvement in at least two of pain, function, or patient global assessment that was 10 mm or more on a 100 mm VAS.

Application site reactions occurred almost uniquely in patients using active topical diclofenac. Dry skin (27%), rash (12%), and pruritus (6%) were most common. Gastrointestinal adverse events occurred in both groups, but with oral diclofenac they occurred significantly more often for dyspepsia, abdominal pain and diarrhoea (Table 1). These gastrointestinal adverse events were also more likely to be severe with oral than topical diclofenac (Table 1). Overall, the number needed to harm (NNH) for severe dyspepsia, abdominal pain or diarrhoea for oral compared with topical diclofenac for 12 weeks was 11 (95% CI 8 to 19). Asthma, dyspnoea and dizziness occurred infrequently, but more commonly with oral diclofenac, while pharyngitis was infrequent and more common with topical diclofenac.

Laboratory changes were also more common for oral compared with topical diclofenac (Table 2). Elevations in liver enzymes and reduced haemoglobin gave NNH values of 7 to 14 (Table 2). Clinically significant elevations of three times the upper limit of normal or more occurred more frequently with oral diclofenac (1%, 5% and 4% with AST, ALT and GGT) than topical diclofenac (0.4%, 1.1% and 1.4% respectively).

**Table 2: Laboratory adverse events with topical and oral diclofenac**

Adverse event	Number (%) with		Relative risk (95% CI)	NNH (95% CI)
	Topical diclofenac (182)	Oral diclofenac (195)		
Elevated AST	1 (0.5)	15 (7.7)	0.1 (0.01 to 0.5)	14 (9 to 31)
Elevated ALT	5 (2.7)	35 (18)	0.2 (0.06 to 1.4)	7 (5 to 11)
Elevated GGT	8 (4.4)	31 (16)	0.3 (0.1 to 0.6)	9 (6 to 18)
Reduced haemoglobin	5 (2.7)	23 (12)	0.2 (0.1 to 0.6)	11 (7 to 25)
Reduced creatinine clearance	7 (3.8)	17 (8.7)	0.4 (0.2 to 1.04)	

## Comment

These are important milestones in our thinking about the evidence for topical NSAIDs in chronic painful conditions like osteoarthritis of the knee. They provide better evidence that topical NSAID is better than placebo, and augment shorter studies showing that topical and oral NSAIDs have equivalent efficacy. There is substantially more evidence that topical NSAIDs do less harm than oral NSAIDs.

The studies were performed impeccably and were large. They were properly randomised and blinded, and used outcomes recommended by

the latest trial guidelines in osteoarthritis. They paid proper attention to adverse events. If there is a problem, it may be a question of formulation. The DMSO vehicle together with the diclofenac led to many local adverse events, probably more so than seen typically with gels, creams, or sprays.

And it is the adverse effects that are so important. Concentrating on them gives us a better insight into what happens with oral diclofenac, a frequently used NSAID. By now we have become used to the gastrointestinal adverse events, but it is still interesting to see the high rate of 10% of reduced haemoglobin with oral diclofenac, as well as the common elevations in liver enzymes and reduced creatinine clearance.

With doubts about the efficacy of paracetamol in osteoarthritis (Bandolier 128), and concerns about cardiovascular effects of oral coxibs that remain to be fully elucidated, guidelines on treatment will have to be revisited. The growing evidence of efficacy and safety with topical NSAIDs should become part of that process.

### References:

- 1 AA Bookman et al. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled study. Canadian Medical Association Journal 2004 171: 333-338.
- 2 SH Roth, JZ Shainhouse. Efficacy and safety of a topical diclofenac solution (Pennsaid) in the treatment of primary osteoarthritis of the knee. Archives of Internal Medicine 2004 164: 2017-2023.
- 3 PS Tugwell et al. Equivalence study of a topical diclofenac solution (PENNSAID) compared with oral diclofenac in the symptomatic treatment of osteoarthritis of the knee: a randomized controlled study. Journal of Rheumatology 2004 31: 2002-2012.



# DULOXETINE FOR FEMALE STRESS URINARY INCONTINENCE

Urinary incontinence is a problem that may affect as many as a third of adult women. Most common is stress incontinence, involuntary leakage brought on by effort or exertion, or sneezing or coughing. Treatments include pelvic floor muscle training, behavioural therapies, and even surgery. Duloxetine is one of the first pharmacological treatment. There are now four published randomised trials of the 40 mg twice-daily dosing regime [1-4], which offer an opportunity not only to examine efficacy, but also to try and understand how trials in stress incontinence are conducted. Bandolier has performed a swift review, therefore.

## Women in the trials

Women were 18 years or older with troublesome stress urinary incontinence lasting at least three months. They had to have seven or more episodes of stress urinary incontinence every week, where an episode was defined as an easily noticed leakage of urine that wet a pad or clothing, and that occurred with physical stress such as coughing, sneezing, or exercising. They had to have a diurnal frequency of fewer than nine per day, a nocturnal frequency of fewer than three per night, and have no urge incontinence.

Additionally, women underwent objective testing of normal bladder capacity and stress incontinence. The bladder was filled with saline. Women were excluded if unable to tolerate filling to 400 mL , with a first sensation of bladder filling at less than 100 mL, or with no sensation at any time during filling. After filling, both a positive cough test (visible leakage on coughing), and a positive stress pad test (leakage of more than 2 grams) were required.

## Outcomes

The main outcome was incontinence episode frequency, which was recorded in real-time daily diaries for a week before each visit. Two diaries were completed before

randomisation, and one at each of the last weeks of three monthly assessments. Other outcomes were quality of life questionnaires, adverse events, and compliance.

## Trial design

Before randomisation there were three two-week periods, for screening for suitability for entry, and with drug free and placebo periods where diaries were completed. Randomisation was by remote central randomisation, stratified by incontinence frequency. Duloxetine and placebo tablets were identical and taken twice a day for 12 weeks.

## Results

There were four trials [1-4] with 958 women on duloxetine 80 mg daily, and 955 on placebo. Women were aged from 22 to about 80 years, with an average age of about 50 years. The average number of incontinence episodes per week at baseline was 14-18 per week in the trials with an overall average of about 17 episodes per week, and over half of the women had more than 14 incontinence episodes a week.

## Efficacy

Treatment with both duloxetine and placebo reduced the number of incontinence episodes over 12 weeks. The overall reduction was 52% with duloxetine and 33% with placebo, with consistency between trials (Figure 1). Not unsurprisingly there was a similar change in the proportion of women who had a 50% or greater reduction in the number of incontinence episodes (Table 1).

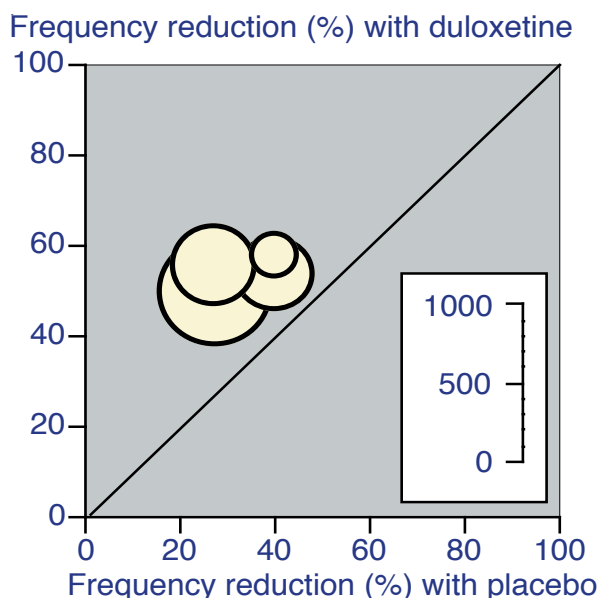
The number needed to treat with duloxetine 80 mg rather than placebo for 12 weeks for one additional woman to have a more than 50% reduction in incontinence episodes was 5.7 (4.5 to 7.8). It was 32 (16 to 765) for one woman to have no incontinence episodes (Table 1).

Quality of life measures used in the trials all showed significant improvements for duloxetine compared with placebo. These included avoidance and limiting behaviour,

**Table 1: Benefits and harms in randomised trials of duloxetine in stress incontinence in women**

Outcome	Number of		Percent of		Relative benefit or risk (95% CI)	NNT/NNH (95% CI)
	Trials	Patients	Duloxetine	Placebo		
Benefit						
At least 50% reduction in incontinence episodes	3	1635	54	36	1.5 (1.3 to 1.7)	5.7 (4.5 to 7.8)
No incontinence episodes in last week	3	1432	11	8	1.4 (1.02 to 2.0)	32 (16 to 765)
Harm						
Patients with at least one AE	4	1913	73	55	1.3 (1.2 to 1.4)	5.5 (4.5 to 7.2)
Serious AE	4	1913	2	1	1.8 (0.8 to 3.9)	
Adverse event withdrawal	4	1913	18	4	5.1 (3.6 to 7.3)	6.8 (5.7 to 8.3)
Nausea	4	1913	23	4	6.4 (4.5 to 9.1)	5.2 (4.6 to 6.2)
Fatigue	4	1913	12	4	3.4 (2.3 to 4.9)	12 (9 to 16)

**Figure 1: Percentage reduction in weekly incontinence frequency with duloxetine and placebo**



psychological impact, and social embarrassment, quality of life measures specific to urinary incontinence.

## Harm

The majority of women reported having at least one adverse event over the 12 weeks (Table 1). About one patient in five on duloxetine withdrew because of adverse events, but few adverse events were described as serious, and these were not significantly higher for duloxetine over placebo (Table 1).

The most common adverse event was nausea (NNH 5), which was moderate or severe in about half the cases. Other common adverse events were fatigue (12%, NNH 12), dry mouth (13%), insomnia (13%), constipation (11%), headache (10%), dizziness (10%), somnolence (7%) and diarrhoea (5%).

## Comment

Duloxetine pharmacology involves effects on serotonin and noradrenaline, so the adverse effects seen in the trials were much to be expected. The effect on stress incontinence was large, with over half the women given duloxetine experiencing a major reduction in stress incontinence events. Given the starting point of about 17 episodes a week, the median reduction was by about eight or nine episodes a week, or one a day.

The NNT of 5.7 was not startling, because there was also a large effect in women given placebo, where a third had a reduction in episodes of more than 50%. This should not be seen as the power of placebo to cause these effects, or mind over matter. It is more likely to be a reflection of the nature of the trials themselves, and the stringent entry requirements that may have maximised the size of the problem, creating conditions where doing nothing was beneficial.

What we have is four high-quality trials that describe a new drug treatment. They give us much information about effect

and common adverse effects. There was some inconsistency of reporting, but that happens when information is compressed into the word limits demanded of scientific papers, so we have a more fuzzy picture than may have been.

The key will be to establish just which women seen in urology clinics or general practice would benefit, and which would find the adverse event profile bearable.

## References:

- 1 PA Norton et al. Duloxetine versus placebo in the treatment of stress urinary incontinence. *American Journal of Obstetrics and Gynecology*. 2002 187: 40-48.
- 2 RR Dmochowski et al. Duloxetine versus placebo for the treatment of north American women with stress urinary incontinence. *Journal of Urology* 2003 170: 1259-1263.
- 3 RJ Millard et al. Duloxetine vs placebo in the treatment of stress urinary incontinence: a four-continent randomised clinical trial. *BJU International* 2004 57: 54-61.
- 4 P van Kerrebroeck et al. Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence. *British Journal of Obstetrics and Gynaecology* 2004 111: 249-257.

## INTERNET DIABETES MONITORING

Considerable effort goes into outpatient clinics, where patients with chronic diseases return at intervals for monitoring or advice. Very often samples are taken for tests, and more visits are needed or letters are written. It really is a great deal of work for professionals and healthcare systems, and effort and fuss for the patients. What if someone invented a way of communicating over the telephone system using television, when patients could monitor their own condition at home? It's called the Internet, and randomised trials of Internet interventions are beginning to emerge [1].

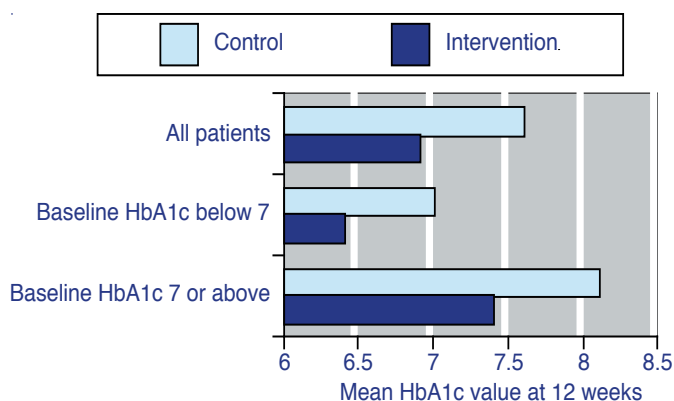
## Trial

The setting for this trial was Korean patients with type 2 diabetes and Internet access. Severe concomitant disease was an exclusion criterion, or previous participation in any similar programme. Participants underwent examination and laboratory tests before and after 12 weeks in the study.

Patients consenting to participate were randomised to usual or Internet care. Usual care involved monthly visits with two or three visits with senior staff during a 12 week period. The Internet intervention consisted of a portal in which patients could enter pre- and postprandial blood glucose results, with information on type and dose of glucose lowering drugs, weight, exercise, and any other important changes. There was also an opportunity to ask questions.

Participants in the intervention group were encouraged to use the Internet three times a week, and participants in both groups were given a supply of monitoring sticks. At the hospital results were examined and a multidisciplinary team provided electronic responses with recommendations regarding medicines according to extant Korean guidelines.

**Figure 1: HbA1c levels in Internet users and usual care controls**



## Results

One hundred and ten patients were randomised, with 101 completing the final examination. Most losses to follow up were because patients stopped visiting the centre. At randomisation groups were identical, were two-thirds men, and had an average age of 54 years. In the intervention groups the average number of log-on times per patient was 42, roughly once every two days. These patients asked an average of 14 questions over the 12 weeks.

The average frequency of blood glucose monitoring was twice as high in the intervention group (average 72 sticks used) as in the usual care group (38 sticks), though a few high users probably skewed these results. HbA1c levels were significantly lower in intervention than in control groups, for all completed patients, and those with baseline HbA1c levels below or above 7% (Figure 1). There were no significant changes to lipids or fasting blood glucose between baseline and the end of the study in either group.

## Comment

This is the first randomised trial of the use of the Internet for outpatients Bandolier has seen. The implication is that better management is achieved when patients use electronic access to information, and they seem to be very keen. How this would work over longer periods remains to be seen.

Patients using the Internet monitoring system were certainly motivated. They used twice as many blood glucose strips. We know that increased use of strips in type 2 diabetes leads to lower HbA1c levels (Bandolier 93), and that lower HbA1c levels lead to lower overall costs (Bandolier 84).

There is no economic analysis with the paper. As best one can see, using the Internet meant that outpatient visits were not needed, while patients remained interested in their condition and treatment. What would be the result on hospital staff utilisation and overall costs remains unknown, but it would be brave to bet against it being cost saving to the hospitals and to society.

### Reference:

- 1 HS Kwon et al. Establishment of blood glucose monitoring system using the Internet. *Diabetes Care* 2004 27: 478-483.

## INTERNET ASTHMA EDUCATION

Patient education is seen as being a critical component of quality asthma care, but education is difficult to provide. Typically it has demanded one-on-one effort from professionals, and there simply are not enough, nor are they well enough supported or resourced. Given that major effort should be put into young asthma patients, and that young asthma patients are often highly computer literate, using the Internet would seem to be the obvious way to solve myriad problems at one fell swoop. A randomised trial shows how well it can work[1].

## Trial

The population was children at a clinic in Missouri, under 18 years with a diagnosis of asthma. All children meeting eligibility were invited to participate, and there were no exclusions because of asthma severity.

Randomisation was to control group or Internet participation group. The control group received asthma education as part of usual care, including verbal and printed information, with 26 instruction sheets available. Education was provided by a nurse practitioner with a total time of 1.5 hours over three initial visits, plus more time if needed or at times of management change.

The Internet group in addition had access to a multimedia programme for asthma control and tracking, incorporating vignettes, principles of self-management, and animated lessons. This programme was accessed through the Internet, but only made available during clinic visits, principally to avoid bias in group comparisons. Participants used the programme at every visit.

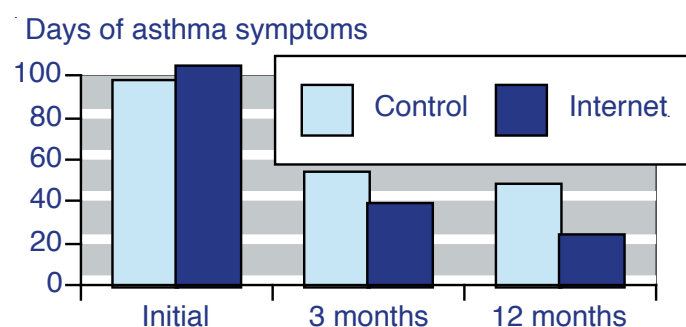
Data were collected at an initial visit, and then at three and 12 months. This included instruments to measure knowledge about asthma for caregivers, and children aged 7-17 years.

## Results

Initially 246 children were randomised, with 228 participating fully. Just under half the children were aged six or below. The two groups were well matched.

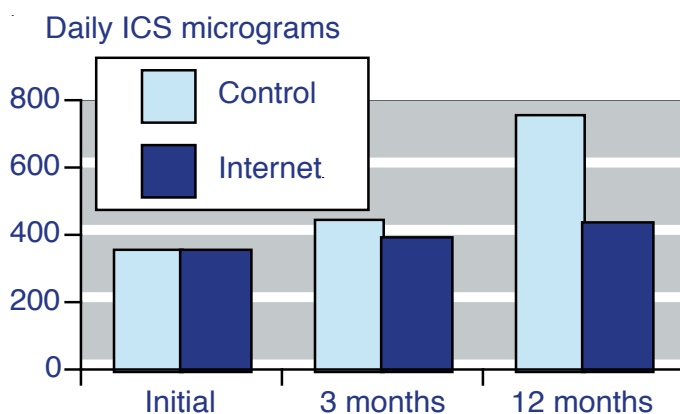
Knowledge scores were higher for caregivers and children aged 7-17 years at three and 12 months in both groups, but

**Figure 1: Asthma symptoms with Internet users and usual care control**





**Figure 2: Inhaled corticosteroid dose in Internet users and usual care controls**



children in the Internet group had higher scores than those in the usual care group.

Children in the Internet and control group had fewer days with asthma symptoms between the first and last visit. With usual care the mean and median reductions were 44 and 17 days, but in the Internet group mean and median reductions were 88 and 58 days. The Internet group had a significantly greater reduction in days with asthma symptoms per year (Figure 1), and this reduction in days with asthma symptoms was achieved with a significantly lower dose of inhaled corticosteroids (by an average of 300 µg/day beclomethasone equivalents, Figure 2).

## Comment

This is another interesting study showing how the Internet could help to deliver better care. In this case access was limited because of a need to avoid contaminating the comparison group. Had the programme been open to children at home to access at any time, the impact might have been greater.

Young asthma patients with more knowledge of their condition, with fewer days of symptoms, and with much less use of inhaled corticosteroid, is something of a holy grail in asthma management. The fact that it can be delivered in a way that is certain to be at relatively low cost using the Internet is a wake-up call to those who want to use IT intelligently. Perhaps a rather more important use of computers than just for storing patient records.

### Reference:

- 1 S Krishna et al. Internet-enabled interactive multimedia asthma educational program: a randomized trial. *Pediatrics* 2003 111: 503-510.

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## COLORECTAL POLYPS: ASPIRIN, COXIBS, AND NSAIDS

Colorectal polyps can occur in people with a history of colorectal cancer, or because they have familial adenomatous polyposis. For both there is laboratory work suggesting that NSAIDs decrease tumours and tumour activity. There is also abundant observational information showing that frequent use of NSAIDs or aspirin is associated with reduced incidence of some cancers.

The next step then is to move from observation to treatment trials. Here the occurrence of frequent colorectal polyps as precursors of later cancers is an ideal early surrogate marker of success. The details of the trials are in Table 1.

### Colorectal adenoma and aspirin

Three trials have examined the efficacy of aspirin versus placebo following colorectal cancer operations, or polyp removal, but with adenomas. These trials were generally large, with about 1,800 patients in total. Trials were properly randomised and double-blinded, and aspirin doses were generally 325 mg daily or less. They were also of long duration, between 30 and 48 months (though for this longer trial there is just a report at one year).

Two of the trials had an absolute reduction in people with at least one adenoma of 10%, while the other showed no difference (Table 1). Overall there was a significant reduction in patients having at least one adenoma with a relative risk of 0.83 (95% CI 0.73 to 0.95). The number needed to treat with 150 to 325 mg aspirin for one to three years for one patient to be free of adenomas was 16 (9 to 56).

One trial had an increased incidence of cardiovascular adverse events with aspirin, with a 1.3% incidence of heart attack and stroke compared with 0.3% with placebo.

### Familial adenomatous polyposis (FAP) and coxibs

Two trials investigated the effect of coxibs on colorectal polyps in patients with FAP (Table 1) over six to nine months. They were randomised and double blind, but small. One showed a large 30% decrease in polyp number and burden with celecoxib 800 mg daily, while there was less effect in a tiny trial with rofecoxib 25 mg daily.

### Familial adenomatous polyposis (FAP) and sulindac

Four small randomised trials have investigated sulindac (usually 300 mg daily) in FAP and its effect on colorectal polyps. All were very small (about 90 patients total), and of four to nine months duration. Three of the four showed a decrease in polyps, while one found no effect. A further trial in young FAP patients who had not developed colorectal adenomatous polyps showed no effect of sulindac on their development over four years.

**Table 1: Trials of aspirin, coxibs, and sulindac in colorectal adenomas and familial polyposis**

Reference	Design	Patients	Treatment	Benefits	Adverse events
<b>Colorectal adenomas: aspirin</b>					
Sandler et al. NEJM 2003 348: 883-890	Randomised, double-blind comparison of aspirin or placebo for a median of 31 months	Colonoscopy for polyp removal within four months, and with colon or rectal cancer with curative surgery. Exclusion was familial polyposis	Aspirin 325 mg daily (N=317) Placebo (N=318)	Median time to first colonoscopy: Aspirin 16 months Placebo 11 months Significantly lower number of adenomas detected with aspirin, with 17% with at least one adenoma with aspirin and 27% with placebo	Adverse events appeared low in number and approximately the same in each group. Death rates similar in both groups
Baron et al. NEJM 2003 348: 891-899	Randomised, double-blind comparison of two doses of aspirin or placebo for a median of 33 months	One or more colorectal adenomas removed within three months, history of at least two confirmed adenomas, or adenoma of at least 1 cm removed in prior 16 months	Aspirin 325 mg daily (N=372) Aspirin 81 mg daily (N=377) Placebo (N=372)	Incidence of one or more adenomas was 47% with placebo, 38% with 81 mg aspirin and 45% with 325 mg aspirin. Bare statistical benefit for lower dose aspirin.	Increased incidence of cardiovascular events (MI, stroke, and revascularisation; 1.3% MI or stroke with aspirin, 0.3% with placebo) with higher dose aspirin than placebo (relative risk about 3). No differences in bleeding, hospital admission, or other cancer incidence.
Benamouzig et al. Gastroenterology 2003 125: 328-336	Randomised, double-blind comparison of aspirin or placebo for 48 months	At least 3 adenomas irrespective of size, or one confirmed adenoma measuring at least 6 mm diameter. Exclusion included familial polyposis, bowel resection	Lysine acetylsalicylic acid 160 mg or 300 mg daily (N=140), or placebo (N=132)	At one-year colonoscopy, at least one adenoma in 38/126 (30%) with aspirin and 46/112 (41%) with placebo. Significant difference for larger adenomas and high grade dysplasia, and total adenomas, though on small numbers	Adverse events were not reported
<b>Familial polyposis: coxibs</b>					
Steinbach et al. NEJM 2000 342: 1946-1952	Randomised, double-blind comparison of celecoxib or placebo for 6 months	Patients with FAP with five or more polyps 2 mm or more in diameter. Exclusion included colectomy within 12 months or anticipated within 8 months, use of NSAIDs or aspirin	Celecoxib 100 mg twice daily (N=32) Celecoxib 400 mg twice daily (N=30) Placebo (N=15)	Higher dose of celecoxib had significant decrease in number of polyps and polyp burden (by about 30%)	No difference in common adverse events. Two patients withdrawn with higher dose of celecoxib (allergic reaction and dyspepsia)
Higuchi et al. Clin Cancer Res 2003 9: 4756-4760	Randomised, double-blind comparison of rofecoxib or placebo for 9 months	Patients with FAP with colorectal polyps.	Rofecoxib 25 mg daily (N=10) Placebo (N=11)	Decrease in number of polyps with rofecoxib (7%) versus increase (3%) with placebo, and significant reduction in polyp size (17%) with rofecoxib	No difference in adverse event rates
<b>Familial polyposis: sulindac</b>					
Labayle et al. Gastroenterol 1991 101: 653-659	Randomised, double-blind comparison of sulindac or placebo for 4 months in each phase of a crossover trial	Patients with FAP with colorectal polyps.	Sulindac 300 mg daily (N=10) Placebo (N=10) One non-compliant patient withdrawn	Sulindac had complete or almost complete regression in 9/9 patients, while with placebo there was an increase in 5, no change in 2, and relative decrease in 2	Not mentioned
Nugent et al. Br J Surg 1993 80: 1618-1619	Randomised comparison over six months	Patients with FAP with colorectal and duodenal polyps who had undergone prophylactic colectomy and with advanced duodenal polyposis	Sulindac Placebo	In 14 patients with rectal polyps, significant polyp regression was seen with sulindac compared with placebo	Not mentioned
Giardello et al. NEJM 1993 328: 1313-1316	Randomised, double-blind comparison of sulindac or placebo for 9 months	Patients with FAP with colorectal polyps, with 18/22 having undergone colectomy	Sulindac 300 mg daily (N=11) Placebo (N=11)	Number and diameter of polyps were 44% and 35% for sulindac. No patient had complete resolution of polyps	No adverse events were noted with sulindac
Ladenheim et al. Gastroenterol 1995 108: 1083-1087	Randomised, double-blind comparison of sulindac or placebo for 4 months	Patients with FAP with colorectal polyps.	Sulindac 300 mg daily (N=22) Placebo (N=22)	No clinically significant regression of sporadic colonic polyps	With sulindac four withdrawals with heartburn (2), anaemia, and urosepsis
Giardello et al. NEJM 2002 346: 1054-1059	Randomised, double-blind comparison of sulindac or placebo for 48 months	Patients had a disease causing mutation in the APC gene but no endoscopically identifiable colorectal adenomatous polyps and no history of surgery. Age 8 years or older (range 8-25 years)	Sulindac 150 or 300 mg daily (N=21) Placebo (N=20)	Four years of treatment did not affect the number or size of adenomas developed	No difference in adverse events. One withdrawal because of neutropoenia

## Comment

Overwhelming evidence for the effect of aspirin, coxib, or NSAID on adenomatous polyp development is lacking. Most of the trials were well done, but most were also small, and there were conflicting results, from excellent to no effect. In FAP, having results in only 90 patients with sulindac trials and 60 in celecoxib trials does not give confidence that we know very much about treatment effects. Longer and larger trials would be needed to do that.

The best evidence, in terms of numbers, for aspirin in colorectal adenomas of non-familial origin, showed that

there was a slight overall effect in 1,617 patients. Statistical significance was achieved, but barely, and the size of the effect was small, though any effect is welcome.

That aspirin is associated with excess strokes and possibly increased risk of myocardial infarction in people at low cardiovascular risk is known. Bandolier 105 reported a review looking at the evidence. The overall picture is obscured by types of study, levels of risk, confounding, and small numbers of events.

This does not help when trying to make decisions about treating colorectal polyps. The jury is still waiting for evidence.